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PATENT COOPERATION TREATY

Applicant : BIO-K PLUS INTERNATIONAL INC. *ET AL.*

International application No. PCT/CA2004/001968

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Priority date : 13 November 2003

Title : USE OF STRAIN OF BACILLUS AND BYPRODUCTS THEREOF
FOR INHIBITING FORMATION OF BLOOD VESSELS

Agent's file reference : 000595-0052

SUPPLEMENTARY AMENDMENT UNDER ARTICLE 34

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To the attention of Ms. Cynthia Brewer

Authorized officer

Madam:

First, the Applicant wishes to thank the Examiner Ms. Brewer for the phone conferences of October 25 and 27 regarding the above identified application.

The instant amendment replaces the "Amendment under Article 34" filed on June 13, 2005 in response to the Written Opinion dated March 14, 2005.

IN THE TITLE

Please cancel the title presently on file and replace it with the following:

"USE OF STRAINS OF LACTOBACILLUS AND BY-PRODUCTS THEREOF FOR INHIBITING FORMATION OF BLOOD VESSELS".

IN THE DESCRIPTION

Please cancel pages 1, 16 and 17 of the description presently on file and insert the new corresponding pages enclosed herewith.

IN THE CLAIMS

Please cancel pages 18 to 21 containing former claims 1 to 31 and insert the corresponding pages containing new claims 1 to 23.

R E M A R K S

MODIFICATIONS TO THE TITLE

Although such as not been requested, the title has been modified to better describe the invention.

MODIFICATIONS TO THE DESCRIPTION :

In response to the Examiner's rejections, the word "Description" appearing on page 1, line 9 of the description has been corrected.

In response to the Examiner's rejection, the numbers of the Figures referred to on page 16, lines 28 and 34 and on page 17, line 3 of the description have also been corrected.

MODIFICATIONS TO THE CLAIMS :

In response to the Examiner's rejection of the claims for lack of novelty and inventive activity, former claim 1 has been limited to a mixture of *Lactobacillus acidophilus*, *Lactobacillus casei* and their broth.

Former claims 24 to 31 have been deleted.

Response to the Examiner's rejection of the claims for lack of novelty in view of D1 to D3

The Applicant has noted the Examiner's rejection of claims 1 to 8, 14 to 26 and 31 for lack of novelty in view of D1 (WO 03/045405), of claims 1, 5 to 10, 12 to 15, 17 to 19, 21 to 24 and 26 for lack of novelty in view of D2 (Arimochi et al.) and of claims 1, 14, 15, 17, 19, 21 and 23 in view of D3 (Kato et al.).

The Applicant submits that claims 24 to 31 have been deleted, thus rendering moot their rejection.

The Applicant also submits that newly submitted claims are now related to a lactic composition for the prevention or the treatment of angiogenesis dependant disorders comprising a mixture of at least a *Lactobacillus acidophilus* strain such as *Lactobacillus acidophilus* I-1492 and *Lactobacillus casei* and their broth.

They are also related to a supernatant obtained from the lactic composition of the invention as an antiangiogenic agent; to the use of the composition of the invention or the supernatant of the invention in the prevention or the treatment of angiogenesis dependant disorders in a mammal; a method for prevention or treatment of an angiogenesis dependant disorder by administering to a mammal the lactic composition or the supernatant of the invention and also to a method of obtaining the supernatant of the invention; whereby the lactic bacterial strains are suspended on a complex MRS medium.

D1 discloses the use of a lactic bacterial strain with the combination of an anti-cancer agent such as 5-fluoro-uracil to treat or prevent cancer, particularly colon cancer. D1 also discloses the use of the supernatant of the lactic bacterial strain in combination with 5-fluoro-uracil to study the apoptosis of cancer cell lines and more particularly, human colon cancer LS 513 cell lines.

D1 does not disclose the lactic bacterial composition comprising a mixture of lactic bacterial strains and their broth, its use as an antiangiogenic; the use of the supernatant of the present invention for treatment or prevention of angiogenesis dependant disorders, nor a method for prevention or treatment of angiogenesis dependant disorders by administering the composition according to the invention to a mammal.

Hence, it is clear from the above that D1 taken alone does not disclose the subject matter of newly submitted claims 1 to 8, 14 to 23.

D2 discloses the use of an animal model in the *in vivo* inhibition of precursor lesions of colon cancer by *Lactobacillus acidophilus* and its supernatant. D2 discloses *Lactobacillus acidophilus* strain ATCC 4356 only. Moreover, according to D2, the lactic bacterial strain is grown on degassed GAM broth. D2 is also silent as to the effect of *Lactobacillus acidophilus* and the supernatant on angiogenesis and angiogenesis dependant disorders.

Hence, it is clear from the above that D2 taken alone does not disclose the matter of the newly submitted claims 1, 5 to 10, 12 to 15, 17 to 19 and 21 to 23.

D3 discloses the ability of *Lactobacillus casei* to reduce the incidence and development of type II collagen induced arthritis in mice which is an animal model of rheumatoid arthritis in humans. Moreover, the *Lactobacillus casei* strain Shirota disclosed in D3 is in solid form and had been re-suspended in

distilled water and had not been incubated in a complex medium before use as it is done in the present invention.

It is thus clear from the above that D3 taken alone does not disclose the subject matter of newly submitted claims 1, 14, 15, 17, 19, 21 and 23.

The Applicant thus submits that it is clear from the above arguments that none of D1, D2 or D3 taken alone discloses the subject matter of the newly submitted claims. Hence newly submitted claims 1 to 23 are new in view of the cited prior art.

In view of the above arguments, the Examiner is kindly requested to reconsider his rejection of the claims for lack of novelty in view of D1 to D3.

Response to the Examiner's rejection of claims 1 to 23 and 27 to 30 for lack of inventive step in view of D1, D2, D4 to D6

A.- The Applicant has noted the Examiner's rejection of claims 1 to 23 for lack of inventive step in view of D2 and D4 to D6.

In this regard the Applicant submits:

D4 teaches that the antitumorogenic activity of *Lactobacillus acidophilus* may be mediated by its direct antagonistic effect against a specific group of organisms. However, this document does not disclose nor teach the composition of the present invention, the activity of the composition of the invention or the supernatant of the invention as an antiangiogenic, as described by the newly submitted claims

Hence, a person skilled in the art, by reading D4 would not be led directly and without undue experimentation to the antiangiogenic composition of the invention nor to its use to prevent angiogenesis dependant disorders.

D5 teaches the use of the genus *Lactobacillus* to prevent a variety of diseases through modulation of the host immune system. D5 discloses the

antitumor, antimetastatic and immunomodulatory activities of *Lactobacillus casei*, both *in vitro* and *in vivo*, but it does not disclose the composition of the invention containing a mixture of *Lactobacillus acidophilus*, *Lactobacillus casei* and their broth, as an antiangiogenic agent, nor it discloses the use of the composition for the prevention or for the treatment of angiogenesis dependant disorders.

D6 is a review article and merely discloses the molecular pathways associated with physiological angiogenesis and reviews pathological angiogenesis, and the relationship of angiogenesis and cancer, diabetes retinopathy and arthritis.

The Applicant submits that none of D4 to D6 teaches the invention as claimed by newly submitted claims 1 to 23.

The Applicant also submits that a person skilled in the art by reading D2 in conjunction with D4 or D5 in combination with D6 would not be led directly and without undue experimentation to the composition or the use of the composition or the supernatant according to the invention since none of D2, D4 or D5 teaches nor suggests the relationship between *Lactobacillus acidophilus* and *Lactobacillus casei* and their broth with angiogenesis, nor do they suggest or teach a method of preventing or treating angiogenesis dependant disorders by using *Lactobacillus acidophilus* and *Lactobacillus casei* and their broth.

In view of the above arguments, the Applicant submits that submitted claims 1 to 23 are inventive in view of the cited prior art.

B.- The Applicant has noted the Examiner's rejection of former claims 27 to 30 for lack of inventive step in view of D1 and D2, and because obtaining a bacterial culture supernatant via centrifugation falls within the scope of routine laboratory practice.

In this regard the Applicant submits that former claims 27 to 30 have been deleted. Thus their rejection has been rendered moot.

Response to the Examiner's other rejection

Finally, in response to the Examiner's rejection of claims 1 to 4 because of the expression "is useful", this expression has been replaced by the expression - - is for - -.

In view of the above Amendment and comments, the Applicant believes that the present application as amended now meets the requirements of the PCT and the invention as now claimed should be held patentable.

Respectfully submitted,

ROBIC

Patent Agents (No. 4078)

ZW/MA/il/cv

Encls.: - Pages, 1, 16 and 17;
 - New pages 18 to 20 of claims.

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